REMARKS

Favorable action on the merits is solicited.

I. CLAIM STATUS AND AMENDMENTS

Claims 1-6 and 8-15 were pending in this application when last examined and stand rejected.

Claim 1 is amended to incorporate the subject matter of claim 2 and part of claim 14. Further support for amended claim 1 can be found in the disclosure, for example, at page 6, lines 25-26, page 7, lines 6-9, Example 2 and the description thereof, including Figures 1-3 at page 9, lines 9-18.

Claim 2 is cancelled without prejudice or disclaimer thereto, because it is now redundant in view of the amendment to claim 1.

Claim 14 is amended to remove the language that was added to claim 1.

Claim 15 is amended to remove the unnecessary "use of" language.

New claim 16 has been added that depends on claim 1 and further specifies that the fraction of sodium hyaluronate having a molecular weight ranging from 50 to 200 kDa is hyalastine as supported by the disclosure, at page 6, lines 25-26.

No new matter has been added by the above claim amendments.

Claims 1, 3-6, and 8-16 are pending upon entry of this amendment.

II. OBVIOUSNESS REJECTIONS

Claims 1-4, 8-9, and 11-15 were rejected under 35 USC §103(a) as allegedly obvious over FRIEDMAN et al. (US 5,744,1555) in view of RILEY (US 5,055,303) for the reasons on pages 3-8 of the Office Action.

Claim 10 was rejected under 35 USC §103(a) as obvious over FRIEDMAN et al. in view of RILEY and further in view of SMOLINSKE (Handbook of Food, Drug, and Cosmetic Excipients, 1992, page 251) for the reasons on pages 8-9 of the Action.

Claims 5 and 6 were rejected under 35 USC §103(a) as obvious over FRIEDMAN et al. in view of RILEY and further in view of BONDA (US 6,551,605) for the reasons on pages 10-11.

These rejections are respectfully traversed as applied to the amended claims. The rejections will be addressed together below. It is noted that FRIEDMAN et al. is the primary reference used in each rejection.

First, Applicants will discuss differences between independent claim 1 and the cited references, in particular, the primary reference of FRIEDMAN.

The rejections should fall, because the combined cited prior art references fail to teach, suggest or make obvious all of the limitations of independent claim 1, as required to support

a *prima facie* case of obviousness. In this regard, amended claim 1 recites:

> A water-in-oil W/O microemulsion comprising a retinoid and a phospholipid emulsifier as active ingredient, and sodium hyaluronate, wherein:
>
> the aqueous phase is present at a concentration ranging from 0.5 to 2% by weight;
>
> the phospholipid emulsifier is phosphatidylcholine or soy lecithin, and is present in an amount ranging from 10 to 15% by weight;
>
> the sodium hyaluronate is a fraction having a molecular weight ranging from 50 to 200 kDa, and is present in an amount ranging from 0.001 to 0.01% by weight; and
>
> the ratio of molar water concentration to molar lecithin concentration (W/lec) is 3.

It is believed that the cited prior art references fail to disclose or suggest each and every element of claim 1.

1) Concentration of the aqueous phase

FRIEDMAN teaches (see col. 8, par. 5.6) that the aqueous phase contains a buffer and that the pH must be adjusted by addition of base (NaOH) so as to avoid formation of complexes, which might disrupt the emulsion (co. 10, lines 5-10). By contrast, in the examples of present application and claim 1, hyaluronic acid sodium salt is directly added to the aqueous phase and no pH adjustment is required.

Further, amended claim 1 recites: “the aqueous phase is present at a concentration ranging from 0.5 to 2% by weight.” By contrast, in FRIEDMAN, an amount of water lower than 5% is

typical of a dehydrated form (see col. 8, par. 5.7) which must be rehydrated before use. This means that the emulsions of FRIEDMAN contain more than 5% water. Thus, it is clear that the FRIEDMAN fails to disclose or suggest the concentration of the aqueous phase in the water-in-oil W/O microemulsion of claim 1.

2) Type and concentration of emulsifiers

Amended claim 1 recites: "phospholipid emulsifier is phosphatidylcholine or soy lecithin, and is present in an amount ranging from 10 to 15% by weight." It should be noted that this amount of surfactant (phosphatidyicholine or lecithin) is significantly higher than that of FRIEDMAN. In this regard, FRIEDMAN, at col. 5, lines 30-31, states: "Usually, the surfactant is present in a proportion of 0.01 to 5% (w/w) of the emulsion, preferably 0.05 to 2%".

Thus, it is clear that the FRIEDMAN fails to disclose or suggest the amount of phospholipid emulsifier (phosphatidylcholine or soy lecithin) in the water-in-oil W/O microemulsion of claim 1.

3) Hyaluronic acid

On column 7, lines 3-16 of FRIEDMAN, hyaluronic acid is mentioned among a list various macromolecules, which are used at a final concentration of 0.0 1-05% w/vol (col. 7, lines 1 & 18). FRIEDMAN also states that the preferred bioadhesive or mucoadhesive macromolecules have a molecular weight of at least

50 kDa, preferably at least 300 kDa and most preferably at least 1000 kDa (col. 7, lines 54-56).

However, there is nothing in FRIEDMAN that would suggest the selection of hyaluronic acid, in particular, the fraction known as Hyalastine, having a molecular weight ranging from 50 to 200 kDa of amended claim 1 and new claim 16. Thus, it is believed that FRIEDMAN fails to disclose or suggest use of hyaluronic acid having a molecular weight ranging from 50 to 200 kDa of amended claim 1, known as Hyalastine of new claim 16.

4) W/lec = [Molar water concentration]/[molar lecithin concentration]

FRIEDMAN fails to disclose or suggest a W/lec ratio is 3 of amended claim 1. FRIEDMAN mentions nothing with respect to this ratio or its significance.

In view of the above, FRIEDMAN fails to disclose or suggest each and every element of claim 1, including: (i) "aqueous phase is present at a concentration ranging from 0.5 to 2% by weight"; (ii) phospholipid emulsifier is phosphatidylcholine or soy lecithin, and is present in an amount ranging from 10 to 15% by weight; (iii) use of hyaluronic acid having a molecular weight ranging from 50 to 200 kDa of amended claim 1; and (iv) W/lec ratio is 3 of amended claim 1. For these reasons, it is clear that independent claim 1 is novel and patentable over FRIEDMAN.

In addition, as noted in the last response, FRIEDMAN fails to disclose or suggest water-in-oil microemulsions containing retinoids, a phospholipid emulsifier and sodium hyaluronate with such properties. Indeed, as acknowledged at the top the bottom of page 5 of the Office Action, "Friedman et al. does not specifically disclose a water-in-oil type microemulsion."

Yet, even if FRIEDMAN discloses oil-in-water emulsions similar to the water-in-oil emulsions of the present application in terms of amounts and type of ingredients, such emulsions contain hyaluronic acid as a mucoadhesive polymer, because they are intended for administering a drug on a mucosal surface. See, claim 1 of FRIEDMAN. FRIEDMAN never mentions the use of sodium hyaluronate in a water-in-oil microemulsion to promote percutaneous absorption.

Further, it is noted that in the water-in-oil microemulsions of the present invention, hyaluronic acid is necessary in order to increase the bioavailability of the active principle by increasing percutaneous absorption. See, for instance, page 12, table and lines 18-22, of the instant disclosure.

In the present invention, it is also pointed out that hyaluronic acid has a viscosizing effect and that the emulsions are preferably applied to skin for treating hyperproliferative diseases, such as acne, psoriasis and lichen planus.

The primary reference of FRIEDMAN fails to disclose or suggest water-in-oil microemulsions with such properties. In fact, none of the cited references, including the secondary references of RILEY, SMOLINSKE and BONDA, disclose or suggest such properties of the present invention.

Indeed, it is believed that none of the secondary references of RILEY, SMOLINSKE, and BONDA fail to remedy the above-noted deficiencies of FRIEDMAN.

RILEY relates to controlled-release bioadhesive systems whose properties vary along with temperature. In RILEY, the systems are solid at room temperature and melt at body temperature (see, column 1, lines 56-57 and column 4, line 43) and they are intended mainly for rectal administration. As such, the systems of RILEY are not thermally stable as in the present invention. By contrast, a main feature of the water-in-oil microemulsions of the present invention is thermal stability.

SMOLINSKE relates to a discussion of the use of parabens in drugs and cosmetics. It does not disclose or suggest their use in water-in-oil microemulsions as in the present invention.

BONDA discusses the use of retinoids. BONDA also discloses how to solubilize and stabilize isoretinoin by means of naphthalene derivatives. However, BONDA does not teach or suggest the use hyalurnoic acid for stabilizing water-in-oil

microemulsions containing retinoids, according to the present invention.

Therefore, it is respectfully submitted that RILEY, SMOLINSKE and BONDA fail to remedy the above-noted deficiences of FRIEDMAN.

For these reasons, it is believed that independent claim 1 is novel and patentable over any combination of FRIEDMAN in view of RILEY, SMOLINSKE and BONDA.

Second, as noted in the last response, the primary reference of FRIEDMAN fails to disclose or suggest water-in-oil microemulsions with specified amounts of ingredients and certain properties. Instead, FRIEDMAN relates to emulsions. Again, emulsions clearly differ from microemulsions for the reasons set forth in the last response. Applicants respectfully submit that, given the known differences, the combined the cited references would not have yielded predictable results to arrive at the claimed water-in-oil microemulsions containing retinoids, a phospholipid emulsifier and sodium hyaluronate in the specified amounts of claim 1.

Applicants respectfully disagree with the Examiner's position on page 7 of the Office Action that the term "microemulsion" (as used in the claims) and the term "emulsion" (as used in the cited references) are interchangeable. They are not. Indeed, as noted in the last response, there are clear structural and functional differences between "emulsions" as used

in FRIEDMAN and RILEY and the term "microemulsions" of claim 1, which goes beyond particle size. Please see again, the attachments in the last response. Again, an emulsion is a mixture of two immiscible substances. Emulsions tend to have a cloudy appearance, are unstable and tend to revert to the stable state of oil separated from water. By contrast, microemulsions are stable ternary systems made of an oily phase, water and a surfactant and are thermal dynamically stable. There are clear structural and functional differences between the two terms as further discussed on pages 3-4 of the instant specification.

Thus, as evidenced by knowledge in the art as shown in the references attached to the last response and the discussion in the instant specification, use of the term microemulsion, rather than emulsion (as done in the cited references), is significant, because such terms denote different properties and structures. Thus, contrary to the Examiner's position, they are not interchangeable, as the two terms do not constitute a mere substitution of one known element for another to obtain predictable results.

Third, at the top of page 7 of the Office Action, the Examiner argues that the argued characteristics are inherent features of the composition. Applicants respectfully disagree and submit that the properties of the claimed microemulsion are the result of the specified ingredients in the amounts claimed. It is believed that the prior art does not disclose the combination of

the claimed ingredients in the specified amounts. Thus, the properties of the claimed composition are not an inherent feature in the composition of the cited references. This is further explained below.

The Examiner's attention should be drawn to the fact that the selection of specific ingredients in specific amounts allows to obtain microemulsions having the chemical-physical properties set out on page 3 , lines 18-26 of the application, which allow for increasing bioavailability of retinoids with respect to conventional formulations (emulsions included). Again, Applicants again note the differences between emulsions and microemulsions, as explained above and in the last response. Again, the compositions of FRIEDMAN are emulsions, not microemulsions.

In order to obtain microemulsions it is necessary to optimize the viscosity of the compositions. The data contained in the application, in particular, that illustrated in figures 3 and 4-6, demonstrate that a W/lec ratio of 3 is critical (of claim 1). When this parameter is satisfied, the viscosity ranges from 1500 to 1750 mPas, as shown in figure 3. None of the cited prior art references disclose or suggest this essential feature of claim 1.

In this regard, the compositions of FRIEDMAN have a viscosity ranging from 1.6 to 18.6 cP (see table 4). Since 1 cPa = 1 mPas (as explained in the citation from Wikipedia attached

herewith as enclosure 1), the compositions of the claims have a viscosity that is 100 fold higher than the compositions in FRIEDMAN. See table 2 in FRIEDMAN which also shows that emulsions with and without carbopol have a slightly higher viscosity than that of water (= 1). Based on such, it is believed that the microemulsions of the claims invention have a remarkably higher viscosity than water and that nothing in FRIEDMAN would have prompted a skilled person to select a W/lec ratio of 3 as in claim 1. This is evidence of the unexpected and superior properties of the claimed microemulsions.

As far as bioavailability is concerned, Table 1 of FRIEDMAN reports the pupil diameter decreased after administration of pilocarpine. The maximum decrease is observed when the maximum amount of pilocarpine is released from the formulations, i.e. after 3 hours. Table 3 reports the concentration of Indomethacin in the anterior eye chamber after release from emulsions with and without surfactant (carbopol) The data show that at 0.75 hrs, indomethacin release is 2.04% and 2.99%, respectively, and that at 1 hr, it is 1.86 and 3.35, respectively. The presence of the polymer in the emulsion increases indomethacin penetration by 80% (1.86 : 3.35 = 100:x), while the AUC is 1.6 times higher than that of formulations without polymer (see column 13, lines 34-36). This is evidence of the unexpected and superior properties of the claimed microemulsions.

Figures 46 of the present application show the absorption of fenretinide released over time µg/cm^2) from a microemulsion according to the claims in comparison with an ointment and with a water-in-oil emulsion. It can be observed that after 6 hrs 60-80 µg fenretinide is released from the emulsions of the invention, whereas, after 6 hrs, only 0.1 µg/cm^2 fernetinide is released from the control emulsions. This data shows that it is necessary for the compositions to be in the form of microemulsions having the W/lec ratio of 3. See, also the table on page 12 of the specification clearly shows the difference between control formulations (emulsions) and the microemulsions of the claims. This is evidence of the unexpected and superior properties of the claimed microemulsions.

Finally, the selection of Hyalastine also has a remarkably positive impact on drug release. Enclosure 2 shows a graphic reporting fenretinide release from a formulation containing all ingredients of example 5 but hyaluronic acid (series 1), a formulation containing all ingredients of example 5 plus hyaluronic acid with high molecular weight (1 x 10 Da, series 2), and a formulation according to example 5, which contains Hyalastine (series 3). Since the highest bioavailability is reached in series 3, the choice of a hyaluronic acid with a molecular weight ranging from 50 to 200 kDa is also critical. This is evidence of the unexpected and superior properties of the claimed microemulsions.

All of the above is considered to be evidence of the unexpected and superior properties of the claimed microemulsions over the emulsions of the prior art.

Applicant note that such a selection of a hyaluronic acid with a molecular weight ranging from 50 to 200 kDa is not suggested in FRIEDMAN, nor any other cited reference. On the contrary, FRIEDMAN teaches that hyaluronic acid with a molecular weight of at least 1000 Da is preferred. In this regard, it is believed that FRIEDMAN actually teaches away from the selection of a low molecular weight hyaluronic acid.

For these reasons, it is the amended claims are novel and unobvious over the combination of cited references. Therefore, it is respectfully submitted that the above-noted §103 obviousness rejections are untenable and should be withdrawn.

III. CONCLUSION

Having addressed all the outstanding issues, the amendment is believed to be fully responsive. It is respectfully submitted that the application is in condition for allowance and notice to that effect is hereby requested. If the Examiner has any comments or proposals for expediting prosecution, please contact the undersigned attorney at the telephone number below.

The Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any

overpayment to Deposit Account No. 25-0120 for any additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17.

Respectfully submitted,

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Appendix:

The Appendix includes the following items:

Enclosure 1 - Definition of Viscosity from Wikipedia

Enclosure 2 - Graph